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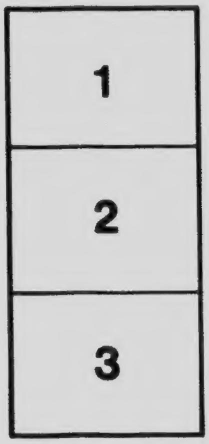

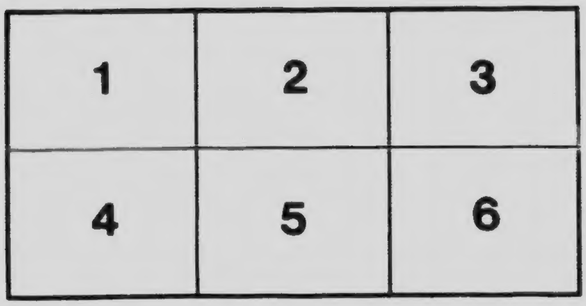

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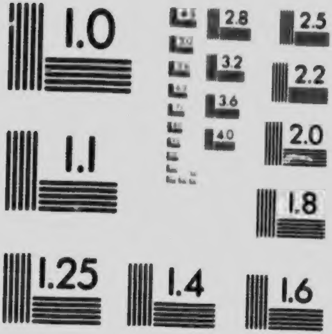

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ADRENALIN VASODILATOR MECHANISMS

FRANK A. HARTMAN, LESLIE G. KILBORN AND LOIS FRASER

From the Department of Physiology, University of Toronto

Received for publication May 24, 1918

From the results of recent work regarding the vasomotor reaction to adrenalin several facts seem to have been established. It has been found that in anaesthetized cats and dogs the arterioles supplying skeletal muscle dilate when small quantities of adrenalin are injected into the circulation and that their reaction changes to constriction when the concentration of adrenalin is sufficiently increased (1), (2). The vessels of the intestinal tract have been found to give the opposite response since they constrict when small, and dilate when large doses are injected (3). It has been shown that there are many parts of the organism, bone (4), skin (5), spleen (3), (6), and possibly kidney (3), (7), the vessels of which show no active dilatation from doses of any strength. It is further conceded by the most recent workers (2), (8),(9) that all blood vessels which are dilated by small quantities of adrenalin lose this reaction, for the time being at least, when separated from central control by cutting their nerves. Dilatation under these circumstances is generally replaced by constriction. The reason for this change in reaction and the whole question of the mechanisms involved are still debated. It has been repeatedly suggested that the conflicting effects of adrenalin in varying concentration are entirely due to its stimulation of neuromuscular junctions of two kinds, one constricting and the other dilating. Those who hold this view believe that vessels which have been recently denervated fail to respond by dilatation to adrenalin because of loss of tone (9), (10).

Work from this laboratory has shown that stimulation of the sympathetic and dorsal root ganglia by adrenalin is sufficient to account for the dilatation (11). Although Gruber has shown that some time after denervation peripheral mechanisms respond in a similar manner, this might be due to loss of sensitivity by the constrictor myoneural junctions. The present research is an investigation of this problem.

METHODS

The methods employed are those of the previous researches described in this Journal, with some modifications and additions. Adrenalin chloride solution (Parke, Davis & Company) was used except in one experiment, in which a more concentrated solution was needed for direct application to ganglia. In this case we used pure adrenalin, made by the same firm. Blood pressure was taken from the carotid artery and injections into the general circulation were made by way of the jugular vein. In order to reduce the constrictor effects of the skin, we eliminated the paw by using a metal cuff open at both ends, a side-tube furnishing connection for the bellows. Both ends of the cuff were made air-tight by packing with a vaseline-cotton or vaseline-paraffin-cotton mixture. In the perfusion experiments, when records were to be taken of one hind limb only we put the cannula into the common iliac artery; when both limb volumes were being recorded we perfused through the abdominal aorta immediately above the bifurcation. The perfusion fluid was allowed to escape through slits in the iliac vein or veins directly into the abdominal cavity since any attempt to lead it away through cannulae from the veins resulted sooner or later in clotting. In some experiments we had difficulty in getting an equal flow of the perfusion solution to the two limbs. Results from these were of course discarded. The difficulty was found to be lessened by tying the internal iliac and the middle sacral arteries. The pressure employed for perfusion varied in different experiments between 10 mm. and 50 mm. Hg., the average being about 20 mm.

In all experiments involving denervation of a limb both the sciatic and femoral nerves were severed. Aseptic precautions were observed in those animals which were to be kept for later use. In none of our experiments did infection of the muscles result. The skin suppurated in a few cases due to post-operative infection, but this seemed in no way to affect the muscle.

In the two experiments (p. 505) in which the changing volume of a limb after denervation was to be continuously recorded as well as its response to periodic doses of adrenalin, we connected the plethysmograph by means of a T-piece to two bellows, one large and one small. The slow changes were recorded on the larger one, while the little one (deflated) was clamped off. When the time came for injection, the clamp was removed from the small bellows tube, the latter bellows being slightly inflated by a small compression of the larger bellows, then the tube leading to the large bellows was clamped. The small bellows was thus prepared to register a small volume change in the limb. After the injection effects were finished, the clamp on the large bellows tube was removed, the small bellows was deflated by forcing the air into the large bellows and then clamped off. By this method no air was lost during the experiment.

RESULTS

Response after recent denervation. The peripheral effect of adrenalin was compared with the total "gangliar peripheral" effect in fifteen cats by studying the volume changes in a denervated limb simultaneously with those in a normal limb (2). The response of the denervated limb was predominantly constriction, although there was a short period of dilatation which usually occurred at the time of the blood pressure rise. Except in a few instances this was undoubtedly a passive effect. In these the dilatation persisted for a short time during the blood pressure fall and came earlier than that in the normal limb (fig. 1, *A*). This dilatation occurred only from small doses of adrenalin, a small increase in the adrenalin being sufficient to obliterate all but a slight passive effect (fig. 1, *B*). On the other hand more than ten times the dose of

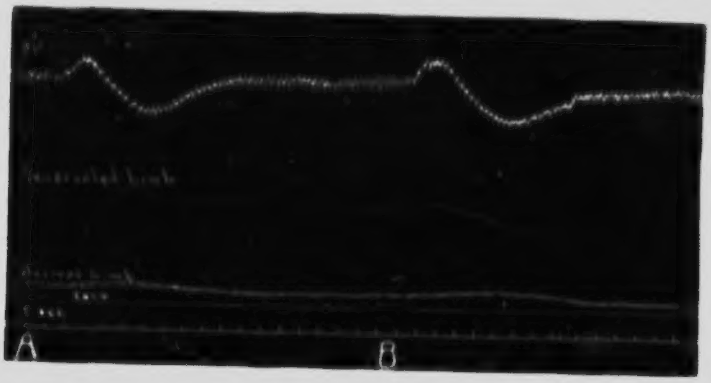

Fig. 1. Small active dilatation (A) of a denervated limb which occurs when 0.2 cc. of adrenalin, 1: 100,000 is given disappears when a slightly larger dose 0.4 cc. of the same solution, (*B*) is injected. Although the bellows for the normal limb was less sensitive, it does show that the maximum dilatation of the normal limb coincides with the maximum fall in blood pressure while the dilatation of the denervated limb does not coincide. Cat, 3.3 kgm. (Reduced one-half)

adrenalin was required to produce constriction in the normal limb as compared with that for constriction in the denervated limb, e.g., constriction in the denervated limb always occurred with doses of about 0.2 cc. to 0.4 cc., 1: 100,000 adrenalin or less, while from 0.3 cc. to 1.0 cc. 1: 10,000 adrenalin was necessary to produce a similar result in the normal limb.

Cutting the nerves to the limb must produce the result described either by removing the influence of the gangliar dilator mechanism or by modifying the blood vessels themselves so that they do not respond through the medium of the peripheral mechanism. From Gruber's work it appears that after some time has elapsed the dilator response to adrenalin develops in the denervated limb. He assumes that this is due to a recovery of tone. In order to test this theory we conducted the following experiments.

After both the sciatic and femoral nerves of one hind limb were dissected out and secured by loose ligatures, the limb was placed in a plethysmograph tube connected to the double bellows system described above. The nerves were severed and the change in volume of the leg registered every five minutes during the remainder of the animal's life. Every hour the response to a depressor dose of adrenalin was determined. In this way the adrenalin reaction could be studied in direct relation to the condition of relaxation or contraction of the vessel walls.

In the first experiment of this kind the animal (cat, 1.8 kgm.) was anaesthetized with ether and lived for eight hours. The limb dilated at an almost uniform rate for the first five hours after the nerves were cut. Dilatation became slower during the sixth hour and had completely stopped at the end, from which time the volume of the limb remained the same until the eighth hour, when the animal died. The blood pressure remained fairly good until a short time before death. The dose of adrenalin used for testing was 0.2 cc., 1: 100,000. Throughout the experiment this produced a fall in blood pressure, preceded by a slight rise. The limb responded by a short dilatation (which may easily have been due to the preliminary blood pressure rise) followed by a more prolonged constriction until the end of the sixth hour when active dilatation appeared. In other words while the limb was in the process of dilating as a result of denervation adrenalin caused constriction, but when the dilatation from this cause was complete a small amount of active dilatation occurred from adrenalin.

In a second experiment where urethane was given, the cat (2.2 kgm.) lived thirty-three hours. The maximum dilatation was reached be-

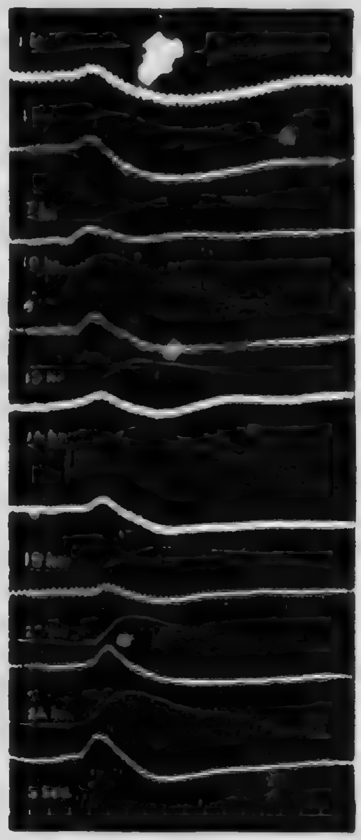

Fig. 2. The response of a denervated limb to a depressor dose of adrenalin during "atonic" and "tonic" conditions. The hours represent the length of time after cutting the nerves. The period of maximum dilatation was reached between the sixth and seventh hours. Up to that time the vessels may be considered "atonic;" after the seventh hour they may be considered "tonic;" 0.5 cc., adrenalin 1: 100,000 was injected in each case. The upper record at each hour represents limb volume, the lower is blood pressure. Cat, 2.2 kgm. Urethane. (Reduced one-half)

tween the sixth and seventh hours. It did not remain long at this level, but constriction soon began, continuing gradually until the twenty-second hour, when it ceased. It remained at this level for the next eight hours. The amount of this remaining dilatation was about one-fifth of the maximum. The dose of adrenalin in each instance was 0.5 cc., 1: 100,000. This usually produced a fall in blood pressure, which was preceded by a rise. During the first five hours adrenalin produced dilatation and constriction of the limb, the dilatation appearing to be largely passive. At the sixth and seventh hours the dilatation became more active and from that time onward the dilator reaction to adrenalin was more pronounced. This was undoubtedly due in part at least to active stimulation, although there was considerable variability in the curves, sometimes the constriction being more pronounced and the dilatation more passive (fig. 2). On the whole it may be said from the two experiments that active dilatation of a denervated limb in response to adrenalin becomes more prominent after the relaxation resulting from denervation has ceased.

In the above experiment we found that a large part of the dilatation resulting from denervation had been recovered from in eighteen hours and that there was little change for the next twelve hours. At this time if the nature of the reaction depends on the condition of tone in the vessels, adrenalin should give good dilatations. In addition to the experiment just described we tried two others. One hind limb was denervated in each of two cats. Eighteen hours later the animal was again anaesthetized with ether and a study made of the adrenalin response, with the following results:

Cat, 2.2 kgm., 0.3 cc., 1: 100,000 adrenalin caused a similar amount of dilatation in both the normal and denervated limbs. Doses of 0.5 cc. to 1.0 cc., 1: 100,000 adrenalin produced either constriction alone or else dilatation and constriction in the denervated limb. Larger doses produced marked constriction in the same limb. Doses as large as 5.0 cc., 1: 100,000 still produced dilatation in the normal limb, moreover these dilatations were much more pronounced than any resulting in the denervated limb. It took 0.8 cc., 1: 10,000 adrenalin to cause a reversal in the normal limb and then it was not complete, dilatation preceding the constriction.

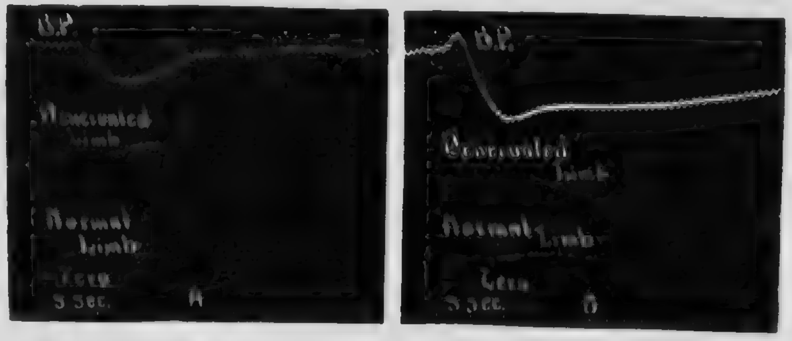

Fig. 3. *A*. Marked active dilatation of a denervated (18 hr.) limb with a small dose of adrenalin 0.2 cc., 1: 100,000. No effect in the normal limb. *B*. Constriction of the same denervated limb with 1.5 cc., 1: 100,000 adrenalin; dilatation of the normal limb. Cat, 2.6 kgm. (Reduced one-half)

Cat, 2.6 kgm., 0.2 cc., 1: 100,000 adrenalin caused a marked dilatation in the denervated limb, but no effect in the normal limb (fig. 3, *A*). Dilatation in the denervated limb, occurred with doses as large as 1.0 cc., 1: 100,000 but 1.5 cc. of the same concentration caused constriction (fig. 3, *B*). Dilatations were not produced in the normal limb until 0.3 cc., 1: 100,000 adrenalin was injected. Dilatation in this limb resulted from doses as large as 0.5 cc., 1: 10,000 adrenalin; however, 0.7 cc. of the latter concentration caused a reversal.

In both experiments the range of dosage for dilatation in the denervated limb was small while quite large amounts of adrenalin were required to bring about reversal in the normal limb. It seems from these experiments that tone may play a part in the response of a denervated limb to small doses of adrenalin. Moreover it appears that the

TABLE 1

A comparison of normal and denervated limbs

ANIMAL	WEIGHT	DURATION OF DENERVATION	DOSE	RESPONSE OF NORMAL LIMB	RESPONSE OF DENERVATED LIMB
	kgm.	*days*	*cc.*		
1. Cat	2.4	7	0.6 A	Dilatation*	Dilatation
			1.0 A	*Dilatation and constriction*	Dilatation
			0.2 B	*Marked constriction*	Dilatation
			0.5 B	*Very marked constriction*	Dilatation
			1.0 B	*Very marked constriction*	*Dilatation and constriction*
2. Cat	3.0	14	0.3 A	Dilatation	Dilatation
			0.4 A	*Constriction*	Dilatation
			0.7 A	*Constriction*	*Constriction*
3. Cat	2.2	15	0.4 A	Slight dilatation	Dilatation
			0.5 B	Slight dilatation	*Marked constriction*
			1.0 B	*Slight constriction*	*Marked constriction*
4. Dog	14.0	22	1.0 A	Dilatation	Dilatation
			1.6 A	Marked dilatation	Marked dilatation
			2.5 B	*Dilatation and constriction*	*Dilatation and constriction*
5. Dog	6.2	31	*0.2 A*	*Nothing*	Dilatation
			0.5 A	*Dilatation and constriction*	Dilatation
			0.2 B	*Dilatation and constriction*	Marked dilatation
			0.5 B	*Very marked constriction*	*Marked dilatation and marked constriction*
6. Dog	5.6	39	0.2 A	Slight dilatation	Slight dilatation
			1.5 A	Dilatation	Dilatation
			5.0 A	*Dilatation and constriction*	Very marked dilatation
			1.0 B	*Dilatation and constriction*	*Dilatation and constriction*

* Unless otherwise stated dilatation means active dilatation.
A = 1: 100,000 adrenalin.
B = 1: 10,000 adrenalin.

peripheral mechanism has a much more limited action than the "gangliar-peripheral" mechanisms when taken together.

After denervation of greater duration. Animals (six dogs and three cats) were studied which had had the sciatic and femoral nerves severed in one limb from seven to thirty days before. It can be seen from the following table (table 1) that although the lapse of a week in most cases renders the peripheral dilator mechanism more effective (see figs. 4 and 5), a greater amount of time does not materially increase the

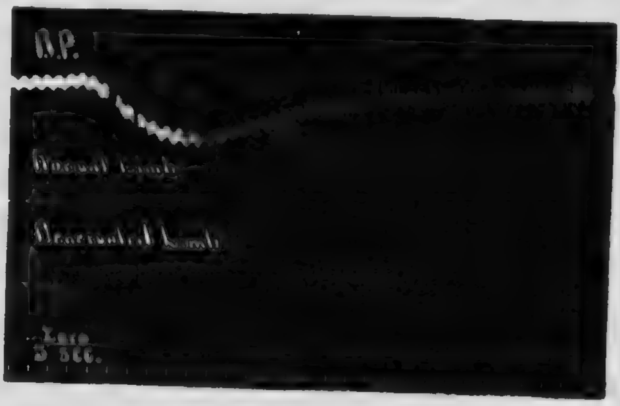

Fig. 4. Dilatation of the hind limb of a cat (2.4 kgm.) to 0.2 cc., adrenalin, 1:100,000, seven days after denervation. (Reduced one-half)

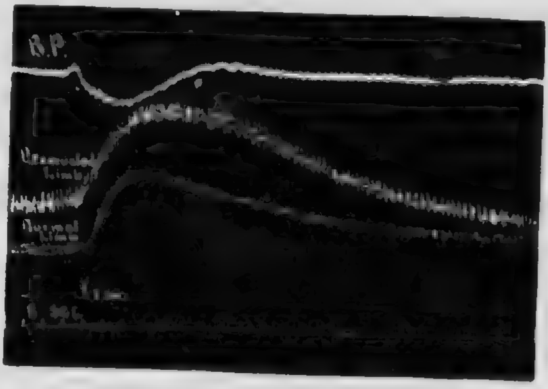

Fig. 5. Dilatation of the hind limb of a dog (14 kgm.) to 0.8 cc. adrenalin, 1:50,000, twenty-two days after denervation. (Reduced one-half)

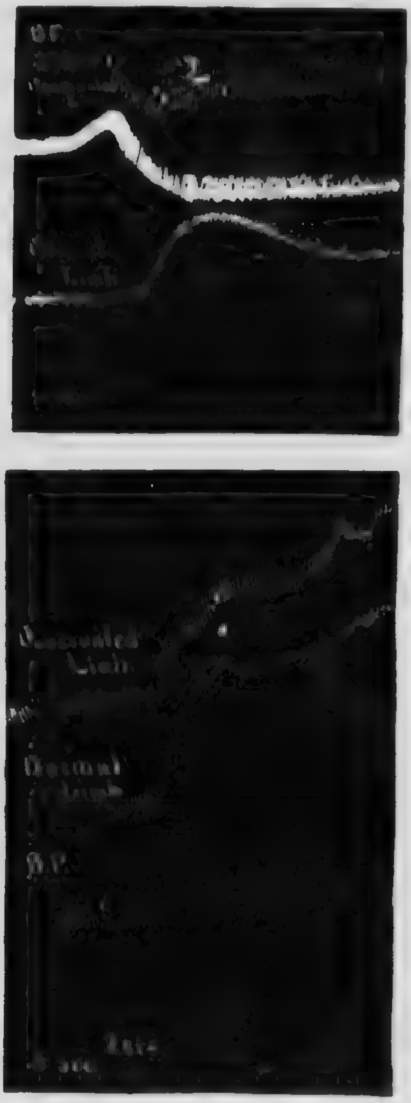

Fig. 6. Reversal of the adrenalin response in a freshly denervated limb by perfusion. Upper record—circulation to limbs intact, 1.0 cc. adrenalin, 1: 10,000 injected into the jugular vein. Lower record—limbs perfused, 2.0 cc. adrenalin, 1: 10,000 injected into the perfusion fluid. Dog 24 kgm. (Reduced one-half)

TABLE 2

Comparison of normal and denervated limbs before and after perfusion

ANIMAL	WEIGHT	DOSE OF ADRENALIN	NORMAL LIMB	DENERVATED LIMB
	kgm.	cc.		
7. Dog	17.0	0.5 A	Dilatation	
		0.3 B	Dilatation	
		0.7 B	Constriction	
		1.0 A	*Dilatation*	
		1.0 B	*Dilatation and constriction*	
8. Dog	15.0	1.3 A	Dilatation and constriction	Small dilatation and marked constriction
		0.5 B	Marked dilatation and small constriction	Marked constriction
		0.7 A		*Marked dilatation*
		0.4 B		*Dilatation and constriction*
		3.0 B		*Pure constriction*
9. Dog		0.5 A	Dilatation	Constriction
		0.4 B	Marked dilatation	Marked constriction
		0.7 B	Dilatation and constriction	Marked constriction
		1.0 A		*Dilatation*
		4.0 B		*Marked dilatation*
		1.0 C		*Dilatation and constriction*
10. Dog	7.5	0.4 A	Dilatation and constriction	Dilatation and constriction
		4.0 A	Dilatation and constriction	Marked constriction
		0.5 A	*Dilatation*	*Dilatation*
		1.0 B	*Constriction*	*Constriction*
11. Dog	24.0	0.5 B	Dilatation	Constriction
		2.5 B	Marked dilatation	Marked constriction
		4.5 B	Dilatation and constriction	Marked constriction
		1.0 B	*Marked dilatation*	*Dilatation*
		5.0 B	*Dilatation and constriction*	*Dilatation and constriction*

A = 1: 100,000 adrenalin.
B = 1: 10,000 adrenalin.
C = 1: 1,000 adrenalin.

Limb perfused where italics are used, injections in that case into the perfusion fluid, otherwise into the jugular vein.

effect. In most cases the constrictor mechanism had become less sensitive as compared with that in the normal limb (see animals 1, 2 and 5, table 1). On the other hand, occasionally the dilator mechanism was easily fatigued so that after a few doses the dilator response disappeared or was considerably decreased.

TABLE 3

*Comparison of perfused limbs of animals in table 1**

ANIMAL	WEIGHT	DOSE	NORMAL LIMB	DENERVATED LIMB
	kgm.	*cc.*		
4 Dog denervated 22 days	14.0	2.0 A	Dilatation	Dilatation
		0.4 B	Dilatation	Dilatation
		1.5 B	Dilatation and constriction	Dilatation and constriction
5. Dog denervated 31 days	6.2	0.05 A	No effect	No effect
		0.1 A	Small constriction	Small constriction
		0.5 A	Dilatation and constriction	Dilatation and constriction
		0.2 B	Dilatation and marked constriction	Dilatation and small constriction
		0.2 B		Marked dilatation
		0.5 B		Very marked dilatation
		1.0 B		Very marked dilatation
		0.5 C		Marked dilatation
		0.8 C		Dilatation and constriction

* Injections into the perfusion fluid.
A = 1: 100,000 adrenalin.
B = 1: 10,000 adrenalin.
C = 1: 1,000 adrenalin.

The dilatation of the denervated limb was no better developed in these animals than in some of the responses from a limb denervated but a few hours before (see fig. 2; 7 hr., 19 hr.). However the dilatation was more constant in occurrence and resulted from a greater range of doses. From the very fact that dilatation quite often takes place in the denervated limb from doses larger than those necessary to produce reversal in the normal limb, it seems that a change has taken place in the myoneural junctions. The constrictor junctions must have lost in sensitiveness or the dilator junctions have gained.

Response of perfused limbs. We have obtained dilatation of both normal and denervated limbs from the injection of adrenalin into the fluid which was perfusing them. A comparison of the perfused normal and denervated limbs injected in this way should help to explain the peripheral dilator mechanism.

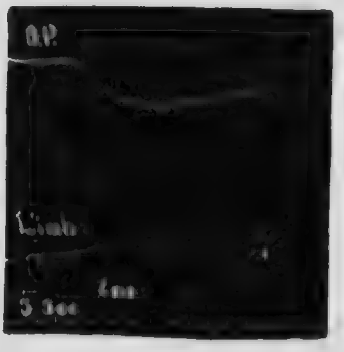

Fig. 7

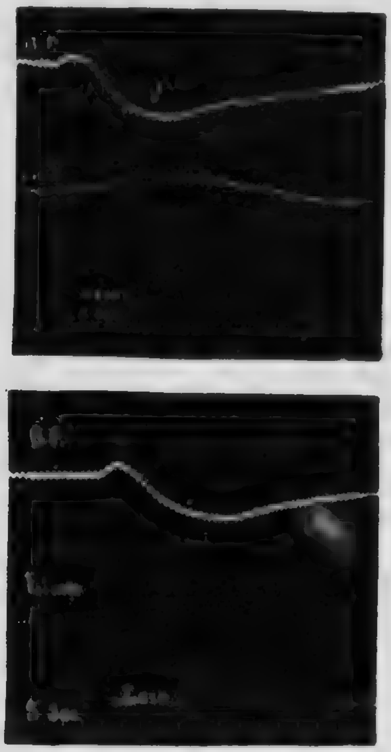

Fig. 8

Fig. 7. Dilatation of a perfused hind limb of a cat by the action of a depressor dose of adrenalin (0.6 cc., 1: 100,000) upon the gangliar portion of the dilator mechanism. Cat 2.4 kgm. (Reduced one-half)

Fig. 8. Dilatation of a hind limb produced by a depressor dose of adrenalin acting upon the gangliar portion of the dilator mechanism. Upper record—response of the hind limb to 0.4 cc. adrenalin, 1: 100,000 injected into the jugular vein, circulation intact. Lower record—response of the same limb to 0.6 cc. adrenalin, 1: 100,000 injected into the jugular vein. (Reduced one-half)

By perfusion of a recently denervated limb an immediate change in the response to adrenalin is brought about, so that dilatation instead of constriction is easily produced (fig. 6 and table 2). This change is similar to that occurring in a denervated limb with normal circulation several hours after denervation (figs. 2, 3, 4, 5 and table 1). The peripheral response to adrenalin in perfused normal and denervated limbs is essentially the same when carried out simultaneously in one animal (animals 10 and 11, table 2). On the other hand there is greater variability in the response of a perfused limb which has been denervated for several days. In one case the constrictors were easily fatigued so that after a few doses of adrenalin they could not again be brought into action except by a dose of 0.8 cc., 1: 1,000 (animal 5, table 3). In another case even perfusion did not bring about dilatation in an animal which had shown no active dilatation with intact circulation (dog, limb denervated eight days). The normal limb gave dilatation before and after perfusion but this is an exceptional case in our experience.

"Gangliar" dilatation from depressor doses. Gruber (9, p. 311) failed to obtain dilatation of a perfused limb from the injection of depressor doses of adrenalin to the general circulation. He infers that the gangliar effect is produced only by pressor doses. We have been able to show in two experiments that depressor doses of adrenalin can bring the gangliar mechanism into action. In both animals a slight increase in the dose was necessary, but the blood pressure response was a pure fall or else a slight rise and decided fall. The animals were cats weighing 2.4 kgm. and 3.0 kgm. In the first, 0.6 cc., 1: 100,000 was required after perfusion (fig. 7). In the second, 0.4 cc., 1: 100,000 caused dilatation before, while 0.6 cc., 1: 100,000 was required after perfusion (fig. 8). When perfusion had gone on for some time even larger doses of adrenalin were required to produce dilatation.

DISCUSSION

The relation of tone to the reversal of adrenalin effects. Recognizing the fact that adrenalin may cause dilatation through both gangliar and peripheral action, we are confronted with the question as to the normal site of dilator action. It has been shown that cutting gangliar connection with the limb in a majority of cases prevents the dilatation of that part. Gruber (9, p. 307) maintains that this is due to a loss of tone in the vessels. In order to understand the development of the tone theory, we should first consider the work of Cannon and Lyman

(10) who were the first to suggest this interpretation for the opposite effects of depressor doses of adrenalin. Their view was reached by the exclusion of other possibilities, viz., (1) central source, (2) blocking of vasoconstrictor impulses, (3) stimulation of vasoconstrictor and vasodilator nerve endings. Their exclusion of the third possibility was on account of the meagre evidence for the existence of vasodilator nerves in the sympathetic system. They found that the blood pressure response was changed to a rise if the tone had been lowered sufficiently by overheating, separation from the central nervous system or by extreme action of the depressor nerve. They attributed vasodilation and vasoconstriction to opposite actions of adrenalin according to the state of the muscle—relaxation when tonically shortened, contraction when relaxed.

Gruber's conclusions were reached because of his inability to obtain dilatation in a freshly denervated limb and the recovery of the dilator response in a limb a few days after denervation. He attributed the reappearance of the dilator reaction to a restoration of tone. It might also be due to a loss in sensitiveness of the constrictor myoneural junctions.

Let us consider, first, the question of tone. In all of our experiments with recently denervated animals the reactions to adrenalin were studied within thirty minutes after denervation and were continued for one or two hours. We have shown above that the maximum dilatation is not reached until the sixth hour after denervation so that those studies were made during the period of steady relaxation. Within this time the usual adrenalin response is constriction, afterwards the reaction begins to reverse (fig. 2). It is not that the vessels have suddenly dilated to their limit and cannot expand further, because they only gradually reach this stage after six or seven hours. Moreover they do not appear to dilate to the limit at any time as a result of denervation because while they are in this state of maximum relaxation, depressor doses of adrenalin often cause further dilatation (fig. 2). We may draw the conclusion that while relaxation is going on the vasodilator myoneural junction is not so easily brought into action and that the constrictor effect therefore predominates.

The state of relaxation seems to affect only the adrenalin receptive substance. Active dilatation of a denervated limb in which the vessels are relaxing can easily be produced by a substance from ox pituitaries (fig 9). In the same animal depressor doses of adrenalin usually caused constriction of the denervated limb (fig. 1).

After denervation of greater duration. A few days after cutting the nerves to a limb, the latter has regained its power to dilate in response to adrenalin so that it does as well as the normal limb. This might be explained by the recovery in tone, but a large part of the tone has been recovered within twenty-four hours, so that the reaction at the twenty-fourth hour should not differ much from that several days later. But it does differ in this respect that in denervations of longer duration it requires much larger doses of adrenalin to cause constriction; in other words, there is a larger range of dosage producing dilatation. In fact a larger dose than that required for the normal limb is needed to bring about reversal in the majority of cases (table 1). Gruber (9, p. 310) also found this to be true. One can interpret this either as a loss in sensitiveness of the constrictor junctions or a gain in sensitiveness of the dilator junctions. The tone theory, however, does not appear to account for this point.

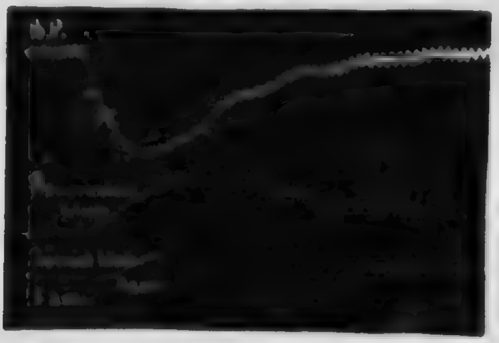

Fig. 9. Dilatation of a freshly denervated limb, produced by a depressor substance obtained from pituitary glands. Cat. (Reduced one-half)

In regard to the question of variation in sensitiveness of the myoneural junctions we have the work of Elliott (12), which indicated that all muscles thrown into contraction by adrenalin have their irritability to this substance increased by denervation. However we have no proof that dilator junctions would be thus affected.

Effects of adrenalin in perfused limbs. A number of investigators have studied the response of various perfused organs to adrenalin with variable results. This would be one of the best methods of proving the existence of vasodilator nerves in the sympathetic if active dilatation could be so obtained.

Employing the change in rate of venous outflow to indicate the vasomotor response Salvioli (14) and Brodie and Dixon (15) obtained only constriction in the hind limb when adrenal extract or adrenalin was added to the perfusion fluid. The latter experimenters found this to be true even in limbs which had been denervated two or three months before. Pari (16) repeatedly obtained an increased outflow from the limb in one experiment when a perfusion of 1:500,000 adrenalin was used, but he inferred that this was due to decomposition products.

Langendorff (17) from his results with rings of coronary arteries concluded that they possessed sympathetic vasodilators which were stimulated by adrenalin. His results were confirmed by Cow (18) and Park (19). Brodie and Cullis (20) from experiments upon perfused hearts concluded that the main cause of adrenalin dilatation was the excitation of vasodilator "nerve-endings."

Langlois and Desbouis (21) obtained constriction in the lung vessels with large doses, 1.0 mgm., and dilatation with small doses, 0.05 mgm. Similar results on perfused lungs were described by Tribe (22).

Other organs have given dilatation from dilute adrenalin perfusing them. For instance, the kidney and the intestine have been found by Ogawa (23) to react in this way. But so far as we know the limb has not been found to react thus when perfused except in the one experiment of Pari (16) and in experiments by Ogawa (23) on the rabbit in which he sometimes obtained dilatation following constriction, but never primary dilatation.

We found it easy to produce dilatation by the injection of adrenalin into the fluid perfusing a limb. Whether the nerves had been cut or not seemed to make no difference in the reaction (table 2).

Why should perfusion reverse the reaction of a denervated limb? Does it mean that perfusion of vessels which were previously relaxing causes them to begin to contract and thus produces the reversal? That might be the condition in perfusion with low pressure (20 mm.) but in a number of our experiments we have doubled or tripled the pressure without materially reducing the dilator response to adrenalin. Moreover Tribe (22) found in the perfused lung that with high pressure it was easier to obtain dilatation than constriction.

Another observation which suggests an explanation of the results just described is the increase in the range of doses of adrenalin which will cause dilatation in both normal and denervated limbs. The interpretation which this seems to suggest is that perfusion renders the constrictor myoneural junction less sensitive or the dilator junctions more sensitive. We have found that it takes much larger doses of adrenalin to bring about constriction in a perfused limb than it did while the circulation was intact, whether it be a denervated limb or one with nervous connections (table 2). For example: whereas 1.0 cc., 1: 10,000 adrenalin injected into the jugular vein before perfusion caused constriction in the denervated and dilatation in the normal limb, 2.0 cc., 1: 10,000 (a dose more than four times as great, considering the limited circulation of the perfusion fluid) injected into the perfusion fluid caused marked dilatation in both limbs (fig. 5). Mechanical effects from the injection were compensated for by a simultaneous withdrawal of an equal quantity of perfusion fluid.

The work of Meyer (13) supports the idea that Ringer's solution modifies the sensitiveness of blood vessels to adrenalin. He found that artery rings kept for some time lost their sensitiveness to adrenalin from day to day and after it had disappeared an opening shock still produced contraction. His results might be due to the changed medium in which the preparations were kept rather than to denervation.

Dilatation from the stimulation of "gangliar" and "peripheral" mechanisms. Before we enter into the discussion of the relative importance of the "gangliar" and "peripheral" mechanisms we wish to call attention to the results of Gruber (9, p. 311), in which he failed to obtain dilatation of a perfused limb from the injection of a small dose of adrenalin into the general circulation. Because the same dose caused dilatation in the intact limb he infers that the dilatation from small doses must be due to peripheral instead of gangliar action. He says:

> If adrenalin exerted its influence entirely through a vasodilator center, it should produce the same results in these two cases where the only difference in the conditions of the limbs is that one has and one has not the circulation intact

This is a very serious difference and might easily account for the increase in the dilator threshold. Oxygenated Ringer's solution or even oxygenated defibrinated blood cannot be expected to fulfil the function of normal blood in all respects and indeed this was not the only difference, for the occlusion of the abdominal aorta interferes with the circulation to the ganglia of the nerves supplying the limbs. The latter condition alone might necessitate a larger dose of adrenalin. If both of these conditions were operative, the dose required would probably in many cases be a pressor dose. However, we have been able to show in two experiments that depressor doses can bring the gangliar mechanism into action. These render unnecessary the assumption of peripheral action to account for dilatation resulting from small doses of adrenalin.

We are not in a position to say which is more important in producing dilatation normally, the "gangliar" mechanism or the myoneural junction. It has been possible in some animals to obtain the same amount of dilatation by the action of adrenalin upon the gangliar portion of the mechanism alone (limb perfused, adrenalin injected into the jugular vein) as occurred from the injection of the same quantity when the circulation of the limb was intact. In many cases, however, larger doses are required to produce equal response in the limb when only the gangliar mechanisms are affected as compared with the condition where both gangliar and periphe[illegible]ctions might be brought into action. This may easily be attributed [illegible] the reduced circulation to the ganglia brought about by clamping the aorta high in the abdomen, but the fact that the peripheral dilator mechanism can be brought into action rather easily under many circumstances indicates that it may well be as important as the gangliar dilator mechanism. At any rate we seem justified in concluding that sympathetic vasodilators to the limb exist and that they are sensitive to adrenalin at the "gan[illegible]" and "peripheral" ends.

We wish to thank R. S. Lang for assistance in th[illegible]h.

SUMMARY

1. While a limb is dilating from denervation adrenalin produces an increase in volume with difficulty, but while the reverse change is taking place the dilator effect of adrenalin begins to reappear.

2. After denervation of a limb, of greater duration, the dilatation from adrenalin occurs from a greater range of doses than is the case in the normal limb.

3. The peripheral action (dilatation) becomes similar in both normal and denervated limbs after perfusion. Under these conditions also dilatation occurs with a greater range of doses.

4. Depressor doses of adrenalin can cause dilatation of a limb by action on the gangliar mechanism.

5. Adrenalin acts on both "gangliar" and "peripheral" mechanisms in producing dilatation of the hind limb.

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CONSTRICTION FROM ADRENALIN ACTING UPON SYMPATHETIC AND DORSAL ROOT GANGLIA

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In the preceding research it has been shown that adrenalin can produce dilatation in a limb by acting upon a "peripheral" mechanism as well as upon a gangliar mechanism. We have been able to show that the constrictor action of this hormone is not confined to the myoneural junction. Although the gangliar response is not easily obtained, it has been found often enough to draw our attention. The methods employed were those described in preceding researches.

All experiments showing constriction from gangliar action must necessarily be those in which the organ tested is completely cut off from the general circulation in order to prevent the peripheral action of adrenalin.[1] Perfusion experiments in which anastomoses to the organ are cut off, satisfy this condition.

Constriction of the limb. Six animals out of nineteen furnished evidence of gangliar constriction in the hind limb. One dog (16 kgm.) and one cat (3 kgm.) gave constriction followed by dilatation when adrenalin was injected into the jugular vein; the first with a dose of 4 cc., 1:20,000 adrenalin, the second with a dose of 5 cc., 1:5,000 adrenalin. In each animal both sympathetic and dorsal root ganglia were intact. On the other hand similar experiments with six dogs and three cats gave no constriction although the usual dilatation could be obtained.

From sympathetic ganglia. Two cats gave positive evidence of a constrictor action of these ganglia by the direct application of adrenalin to them. In the first, a 1: 100,000 adrenalin solution produced only dilatation while a 1: 10,000 solution caused steady marked constriction. In the other a 1: 1,000 solution caused a dilatation followed by constriction. Three animals gave no constriction. The first (a cat) was tried by dropping adrenalin upon the sympathetic ganglia. On the last two (dogs) the dorsal root ganglia had been removed, adrenalin being given by the jugular vein.

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[1] Salvioli (Arch. ital. de biol., 1902, xxxvii, 384) perfused the limb of a dog, with the nerves intact. Adrenal extract was injected into the jugular vein and the volume change in the limb was studied by the venous outflow. He usually obtained no change in the flow but occasionally there was a small decrease in the outflow. This was believed to be due to the escape of adrenal extract into the limb because the decrease was not synchronous with the rise in blood pressure; in fact the pressure had returned to normal before the limb changed.

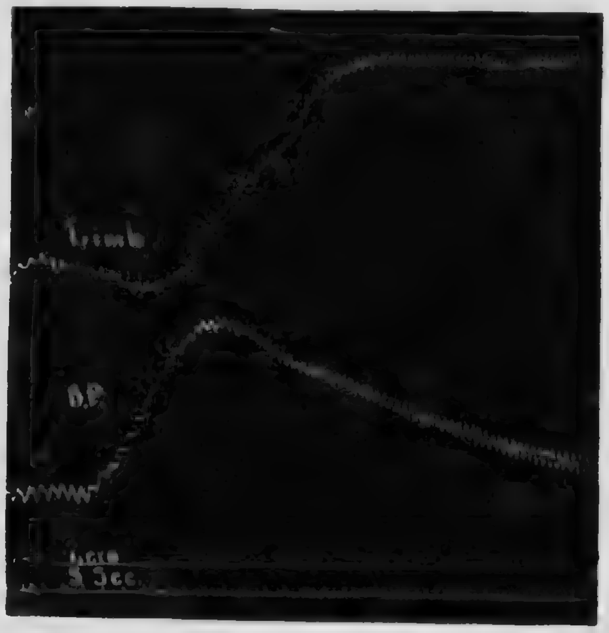

Fig. 1. Constriction and dilatation of a perfused limb from the injection of 4 cc. adrenalin, 1: 5,000 into the jugular vein. All sympathetic ganglia supplying the limb had been destroyed. Dog 21.6 kgm. Reduced ½.

From dorsal root ganglia. Of the animals (seven dogs) in which the sympathetic ganglia to the perfused hind limb had been destroyed, only one responded by constriction when adrenalin was injected into the general circulation (fig. 1). Direct application of adrenalin to the dorsal root ganglia in one of two cats caused constriction in the hind limb (fig. 2). In almost all of the animals studied whether giving gangliar constriction or not, dilatation from adrenalin was obtained.

We may say, in general for the hind limb, that the effect of adrenalin on the ganglia is preëminently dilator and that the constriction from this source is insignificant.

Constriction of the intestine. Constriction of a gangliar source was more common in the intestine than in the limb. A response of this sort was obtained in six out of thirteen animals. Moreover the number of constrictions obtained in the same animal was much greater in the case of the intestine than in the experiments with the limb. In the latter there would often be only one or two constrictions throughout the whole experiment.

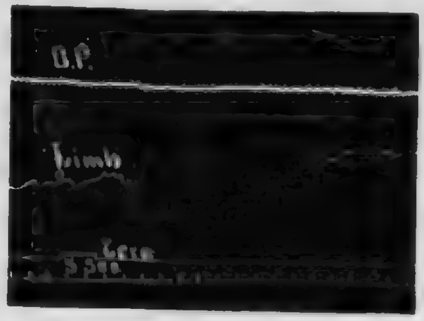

Fig. 2. Constriction of the hind limb resulting from the direct application of 1: 1,000 adrenalin to the lower lumbar dorsal root ganglia. Dog 16 kgm. Reduced ½.

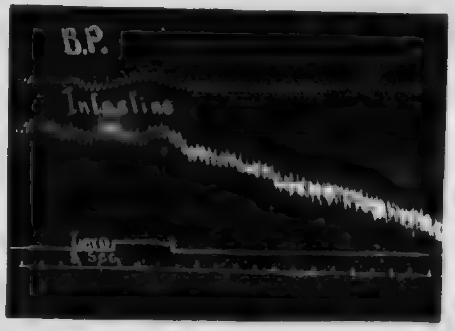

Fig. 3. Constriction of the intestine produced by direct application of 1: 1,000 adrenalin to the twelfth and thirteenth dorsal root ganglia. Dog 11 kgm. Reduced ½

Three dogs whose splanchnic nerves had been cut gave positive evidence of gangliar constriction. The intestinal loop was perfused and the adrenalin was injected into the jugular vein. Both constriction and dilatation occurred whenever the intestine responded by constriction.

Intestinal constriction was also produced by the direct application of adrenalin to the dorsal root and superior mesenteric ganglia.

In a cat although dilatation only had been produced by the application of 1 : 1000 adrenalin to the twelfth and thirteenth thoracic dorsal root ganglia in three instances, in a fourth the same concentration produced constriction followed by dilatation.

Fig. 4. Constriction of the intestine from direct application of 1: 1,000 adrenalin to the superior mesenteric ganglion. Dog. Reduced ½.

In a dog, a 1 : 1,000 solution produced dilatation alone, constriction alone (fig. 3) or constriction followed by dilatation.

Marked constriction of the intestine was caused in another experiment by treating the superior mesenteric ganglion with 1 : 1,000 adrenalin chloride to which a little pure adrenalin had been added (fig. 4).

Additional evidence that the superior mesenteric ganglion is a source of constriction was obtained in one animal by the use of nicotine. Before nicotine, adrenalin caused constriction followed by dilatation of the intestine. Intravenous injection of nicotine ruled out both the constriction and dilatation.

Thus the gangliar effect of adrenalin as far as the intestine is concerned is largely dilator, although it is sometimes a source of constriction.

SUMMARY

1. Adrenalin occasionally produces constriction in the hind limb by its action upon the sympathetic and dorsal root ganglia.
2. Constriction of the intestine is sometimes produced by adrenalin acting upon the superior mesenteric and dorsal root ganglia.

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